Public Assessment Report

Scientific discussion

Gestoden/Ethinylestradiol 75/20 “Stragen”
Gestoden/Ethinylestradiol 75/30 “Stragen”

75/20 micg and 75/30 micg coated tablets

Gestodene/Ethinylestradiol

DK/H/1149/001-002/DC

This module reflects the scientific discussion for the approval of Gestoden/Ethinylestradiol 75/20 “Stragen”/Gestoden/Ethinylestradiol 75/30 “Stragen”. The procedure was finalised on 13 August 2008. For information on changes after this date please refer to the module ‘Update’.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for of Gestoden/Ethinylestradiol 75/20 "Stragen"/Gestoden/Ethinylestradiol 75/30 "Stragen" coated tablets, from Stragen Nordic A/S. The product is indicated for oral contraception.

Gestoden/Ethinylestradiol 75/20 "Stragen"/Gestoden/Ethinylestradiol 75/30 "Stragen" coated tablets are fixed-combination tablets of which combine potent synthetic derivatives of the natural estrogen estradiol and the progestogen gestodene. The tablets are monophasic oral contraceptives containing ethinylestradiol 20 micg/30 micg and gestodene 75 micg as active ingredients. The monophasic combination of ethinylestradiol and gestodene inhibits ovulation via a negative feedback mechansim on the hypothalamus, which alters the normal pattern of gonadotropin secretion of follicle-stimulationg hormone and luteinizing hormone by the anterior pituitary. In addition, the combination oral contraceptive modifies cervical secretions, producing an unfavourable environment for implantation.

The product is indicated in women as oral hormonal contraceptive. An gestodene/ethinylestradiol therapy consists in a single dose of 75/20 or 30 micg given once daily, for 21 days, starting on the first day of the menstrual cycle. No medication is taken during the 7-day menses period.

This repeat use procedure concerns a generic application claiming essential similarity with the reference products Meloden 75/20 micg coated tablets and Gynera 75/30 micg coated tablets by Schering. The reference products have been registered in Denmark since 1995 and 1988, respectively.

The marketing authorisation is granted based on article 10.1 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Each Gestoden/Ethinylestradiol 75/20 "Stragen" coated tablet contains 75 micrograms gestodene and 20 micrograms ethinylestradiol.
Each Gestoden/Ethinylestradiol 75/30 "Stragen" coated tablet contains 75 micrograms gestodene and 30 micrograms ethinylestradiol.

The tablets are white, round, biconvex sugar coated tablets, both sides are without imprinting.

Gestoden/Ethinylestradiol 75/20 "Stragen"/Gestoden/Ethinylestradiol 75/30 "Stragen" is packed in blister packs (PVC/aluminium) in pack sizes of 1 x 21 tablets; 3 x 21 tablets, and 6 x 21 tablets. However, not all pack sizes may be marketed.

The excipients in the tablet core are: Magnesium stearate; povidone K-25; maize starch and lactose monohydrate.

The coating consists of: Povidone K-90; macrogol 6000; talc; calcium carbonate; sucrose and wax montan glycol.

Compliance with Good Manufacturing Practice
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The active substance gestodene is not described in the European Pharmacopoeia. It is a white or yellowish crystalline powder. It is practically insoluble in water, soluble in methylene chloride, slightly soluble in ethanol and methanol. It is optically active. It has six asymmetric carbon atoms. It consists of only one crystalline form.

The documentation on the active substance is presented as a European Drug Master File/Active Substance Master File (DMF) (in CTD-format). The Applicant's Part of the DMF has been forwarded by the Applicant. The Applicant's and Restricted Part plus a LoA has been forwarded by the ASM.

The active substance ethinylestradiol is described in the European Pharmacopoeia. It is a white or slightly yellowish-white, crystalline powder. It is practically insoluble in water, freely soluble in alcohol. It dissolves in dilute alkaline solutions. It is optically active.
The manufacturer of the active substance has obtained a Certificate of Suitability, a copy of which is presented in the documentation.

The control tests and specifications for both drug substances gestodene and ethinylestradiol are adequately drawn up.

Based on the stability data presented, appropriate retest periods have been set.

II.3 Medicinal Product

The finished product is white round biconvex coated tablets, to be marketed in PVC/Alu blister packaging. Each tablet core contains less that 5 % of the active substance gestodene and less than 5 % of the active substance ethinylestradiol.

The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 6 batches of each 'strength'. The batch analysis results show that the finished products meet the specifications proposed.
The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 24 months with 'do not store above 30°C' for the drug product is considered acceptable.

III. NON-CLINICAL ASPECTS

This product is a generic formulation of Meloden and Gynera coated tablets, which are available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application since pharmacodynamic, pharmacokinetic and toxicological properties of gestodene and ethinylestradiol are well known. Overview based on literature review is, thus, appropriate.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of gestodene/ethinylestradiol released into

the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

IV. CLINICAL ASPECTS

IV.1 Introduction

Gestodene and ethinylestradiol are well-known active substances with established efficacy and tolerability.

For this generic application, the MAH has submitted one single-dose bioequivalence study under fasting conditions in which the pharmacokinetic profile of the test product Gestoden/Ethinylestradiol 75/30 "Stragen" is compared with the pharmacokinetic profile of the reference product Moneva 75/30 micg coated tablets, Schering, France.

The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 28 days between the two administrations. Gestodene is highly bound to SHBG which is why 28 days was chosen to allow SHBG to return to normal levels before Period 2. 2 tablets of Gestoden/Ethinylestradiol 75/30 "Stragen" were administered in each period (~2x30 micg ethinylestradiol and 2x75 micg gestodene). 2 tablets were dosed to meet bioanalytial assay requirements although the product labelling specifies a dose of one tablet per day.

Blood samples were collected pre-dosing and at time points up to 96 hours for gestodene and up to 72 hours for ethinylestradiol post administration of a single-dose of 2x75 micg gestodene/30 micg ethinylestradiol fixed combination tablets with 240 ml of water for the analyses of gestodene and ethinylestradiol.

48 healthy post-menopausal, non-smoking, Caucasian female subjects (49-63 years) were enrolled and participated in the study. 48 subjects completed the study. Statistical analysis was carried out on the first 46 subjects to complete the study according to study protocol.

The pharmacokinetic parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, K_{el} $t_{½\ el}$ and residual area. Primary variables were AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

The applicant would conclude bioequivalence if 90% CI were within 80-125% for ln-transformed AUC_{0-t}, AUC_{0-inf} and ln-transformed C_{max} according to the study protocol.

Table 1. Pharmacokinetic parameters of gestodene under fasted conditions.

Treatment N=46	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	52794.80	57546.47	5662.99	0.894	25.87
Reference	52553.32	57701.88	5831.59	0.844	25.74
Ratio[1]	100.44 %	99.94 %	96.22 %		
90% Geometric C.I.[2]	95.82 % to 105.29 %	95.49 % to 104.59 %	92.35 % to 100.24 %		
Intra-Subject CV	13.45 %	13.00 %	11.70 %		

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

[1] Calculated using least-squares means according to the formula $e^{(\text{Ethinylestradiol-Gestodene (A)-Moneva (B)})}$ x 100
[2] 90% Geometric Confidence Interval using ln-transformed data

Table 2. Pharmacokinetic parameters of ethinylestradiol under fasted conditions.

Treatment N=46	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1367.86	1553.45	141.24	1.51	16.79
Reference	1281.11	1456.75	136.14	1.50	16.45
Ratio[1]	106.97 %	107.02 %	104.28 %		
90% Geometric C.I.[2]	103.79 % to 110.25 %	104.06 % to 110.07 %	101.21 % to 107.43 %		
Intra-Subject CV	8.59 %	7.99 %	8.49 %		

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

[1] Calculated using least-squares means according to the formula $e^{(\text{Ethinylestradiol-Gestodene (A)-Moneva (B)})}$ x 100
[2] 90% Geometric Confidence Interval using ln-transformed data

The 90% confidence intervals for the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the acceptance range of 80-125%.
Based on the submitted bioequivalence study Gestoden/Ethinylestradiol 75/20 "Stragen"/Gestoden/Ethinylestradiol 75/30 "Stragen"coated tablets are considered bioequivalent with Meloden 75/20 micg coated tablets and Gynera 75/30 micg coated tablets, respectively, with respect to rate and extent of absorption of gestodene and ethinylestradiol. Tolerability of the test product is acceptable and not significantly different from reference product.

The 75/20 micg strength is dose proportional with the 75/30 micg strength. The pharmacokinetics of the active substances are linear in the dose range. The results of the bioequivalence study performed with the 75/30 micg strength therefore apply to the 75/20 micg strength.

The RMS has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.2 Risk management plan & Pharmacovigilance system

The combination gestodene/ethinylestradiol was first approved in 1995 (75/20 micg) and 1986 (75/30 micg), respectively, and there is now more than 10 years post-authorisation experience with the combination of active substances. The safety profile of gestodene/ethinylestradiol can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

The Pharmacovigilance system described fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the identification and notification of any a potential risks occurring either in the Community or in a third country.

V. PRODUCT INFORMATION

SmPC and Package leaflet
The content of the SmPC and package leaflet approved during the decentralised procedure is in general in accordance with that accepted for Gestinyl (DK/H/0926/001-002/DC, Day 210: 26 January 2007), marketed by Stragen Nordic A/S.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the package leaflet was Danish. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gestoden/Ethinylestradiol 75/20 “Stragen”/Gestoden/Ethinylestradiol 75/30 “Stragen” coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Meloden 75/20 micg coated tablets and Gynera 75/30 micg coated tablets by Schering. Meloden and Gynera are well-known medicinal products with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with that accepted for Gestinyl (DK/H/0926/001-002/DC, Day 210: 26 January 2007), marketed by Stragen Nordic A/S.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Gestoden/Ethinylestradiol 75/20 “Stragen”/Gestoden/Ethinylestradiol 75/30 “Stragen” with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 13 August 2008. Gestoden/Ethinylestradiol 75/20 “Stragen”/Gestoden/Ethinylestradiol 75/30 “Stragen” was authorised in Denmark on 2 October 2008.

A European harmonised birth date has been allocated (1995-03-17 (75/20 micg) and 1986-07-09 (75/30 micg)) and subsequently the first PSUR will be submitted with a DLP of 2009-03 (75/20 micg) and 2009-08 (75/30 micg), respectively, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 13 August 2013.

The following post-approval commitments have been made during the procedure:

- The Applicant commits to reconsider limits for total impurities in the shelf-life specification at the end of stability studies i.e. 36 months.